In the outstanding Official Action, claims 1 and 20 were objected to for containing several informalities. Claims 1 and 20 were objected for containing typographical errors. It is believed that the present amendment addresses these objections. Applicants would like to thank Examiner Young for her attention to detail in this matter.

Claims 1-21 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-21 of co-pending Application No. 09/787,887. This rejection is traversed.

Enclosed with this amendment is a terminal disclaimer directed to Application No. 09/787,887. It is believed that the terminal disclaimer obviates the double patenting rejection.

In the outstanding Official Action, claims 1-21 were rejected under 35 USC 103(a) as allegedly being unpatentable over NYSTROM in view of knowledge in the art. This rejection is respectfully traversed.

Applicants respectfully submit that the Official Action uses an impermissible approach in determining whether the claimed invention is obvious over NYSTROM in view of the knowledge in the art at the time the application was filed. In imposing the rejection, the outstanding Official Action dissects the claims into allegedly essential elements and non-essential elements. Applicants traverse the dissection of the claims in this manner.

It is believed that categorizing the recitations of the claims as essential and non-essential is improper.

Applicants note that 35 USC 103(a) provides that the subject matter of the claimed invention "as a whole" must be considered. Moreover, *Graham v. John Deere Co.*, 383 US 1, 148 USPQ 459 (1966) establishes the following considerations for determining obviousness under 35 USC 103(a):

(1) determining the scope and contents of the prior art;

(2) ascertaining the differences between the prior art and the claims at issue;

(3) resolving the level of ordinary skill in the pertinent art; and

(4) considering objective evidence present in the application indicating obviousness or non-obviousness.

Thus, it is clear that the relevant case law and statute fails to make any reference to dissecting a claim on the basis of its essential and non-essential elements. As such, it is respectfully submitted that the outstanding Official Action fails to utilize the appropriate test for determining obviousness under 35 USC 103(a).

Applicants further submit that the teachings of NYSTROM in view of the knowledge in the art at the time the application was filed, would not lead one of ordinary skill in the art to the claimed invention.

Applicants believe that it would not have been obvious to one of ordinary skill in the art to utilize ordered interactive mixtures in combination with mucoadhesive promoting agents. As noted in the present specification on page 4, applicants have unexpectedly discovered that an ordered mixture may be utilized in the sublingual administration of an active ingredient. However, at the time the application was filed, one of ordinary skill in the art would have expected that an ordered mixture requires a relatively large volume of liquid in order to be effective. However, in the sublingual administration of an ordered mixture, the volume of liquid available as a solvent is limited to just a few millimeters. Thus, it cannot be said that it would be obvious to one skilled in the art to utilize an ordered mixture in a sublingual administration of an active ingredient.

Moreover, applicants note that NYSTROM fails to mention muco- or bioadhesive components. In fact, NYSTROM fails to disclose or suggest a combination of ordered mixtures and mucoadhesive agents. Moreover, applicants note that one of ordinary skill in the art would appreciate that microcrystalline cellulose does not exhibit bio/mucoadhesive properties. While it is true that this is stated in the specification and claims, applicants have amended the claims and specification to correct this obvious error.

Mucoadhesion promoting agents have been used to significantly increase the time period for drug release at a specific absorption site. For example, buccal tablets and gel formulations have been utilized to obtain the extended release of drugs into the body.

However, for these types of systems, it is the entire dosage form that exhibits the mucoadhesive properties. In the present invention, the dosage form does not have to remain intact (slowly releasing its content of drug), but it can quickly disintegrate to a large number of mucoadhesive subunits, which can attach to the sublingual mucosa for a relatively short period of time.

Thus, the mucoadhesive promoting agent in the present invention is not just "added to the composition" resulting in general mucoadhesive properties of the entire coherent dosage form, but rather, the mucoadhesion promoting agent may be added in a particulate form.

In an effort to remedy the deficiencies of NYSTROM, the Official Action alleges that the "knowledge in the art" in combination with the teachings of NYSTROM renders obvious the claimed invention. However, the publications cited in the Official Action as being representative of the "knowledge in the art" at the time the application was filed, fail to disclose or suggest claimed pharmaceutical composition or claimed method.

As conceded by the Official Action, NYSTROM fails to disclose or suggest the claimed active agent, the constituents of the carrier compound and the therapeutic effects of the composition. While the Official Action contends that these individual components may be found within the "knowledge of the art", applicants note that because a publication may disclose one of several recitations of a claim, it does not follow that the claim as a whole is rendered obvious.

In other words, while the Official Action states that the FINE et al. and the STANLEY patents disclose individual components of the claimed invention, it is believed that these publications fail to provide one of ordinary skill the motivation and reasonable expectation of success of modifying their respective teachings to obtain the claimed invention. As a result, applicants believe that the proposed rejection fails to establish a *prima facie* case of obviousness.

With regard to claims 5, 9 and 21, the Official Action contends that the specific concentrations and dosages for the composition are non-critical and obviated by the prior art. In support of this contention, the Examiner cites *In re Aller* 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955) and *In re Russell* 439 F.2d 1228, 169 USPQ 426 (CCPA 1971). However, applicants traverse this contention.

As the Examiner is aware, a particular parameter must first be recognized as a result-effective variable, i.e., a

variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation or what may be well known in the art. *In re Antoine*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). None of the cited publications in the outstanding Official Action disclose or suggest that the components set forth in the claimed invention may act as result-effective variables. Thus, it is respectfully submitted that it would not be obvious to one of ordinary skill in the art to optimize the claimed ranges and dosages.

In view of the present application and the foregoing remarks, therefore, it is believed that this application is onw in condition for allowance, with claims 1-21, as presented. Allowance and passage to issue on that basis are accordingly respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Page 7, the paragraph beginning on line 1 has been amended as follows:

--A variety of polymers known in the art can be used as bio/mucoadhesion promoting agents. In addition to their polymeric nature, their ability to swell is important. On the other hand, it is also important that they are substantially insoluble in water. Their swelling factor by volume when brought into contact with water or saliva should preferably be at least 10, while a factor of at least 20 is more preferred. Examples of such bio/mucoadhesion promoting agents include cellulose derivatives such as hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose and sodium carboxymethyl cellulose (NaCMC); starch derivatives such as moderately cross-linked starch; acrylic polymers such as carbomer and its derivatives (Polycarbophyl, Carbopol®, etc.); polyethylene oxide (PEO); chitosan (poly(D-glucosamine)); natural polymers such as gelatin, sodium alginate, pectin; scleroglucan; xanthan gum; guar gum; poly co-(methylvinyl ether/maleic anhydride); [microcrystalline cellulose (Avicel®);] and crosscaramellose. Combinations of two or more bio/mucoadhesive polymers can also be used. More generally, any physiologically acceptable agent showing bio/mucoadhesive

characteristics may be used successfully to be incorporated in the carrier. Bio/mucoadhesiveness can be determined in vitro, e.g. according to G. Sala et al., Proceed. Int. Symp. Contr. Release. Bioact. Mat. 16:420, 1989.--.

IN THE CLAIMS:

Claim 1 has been amended as follows:

--1. (amended) A pharmaceutical composition for the treatment of acute disorders by sublingual administration, comprising an essentially water-free, ordered mixture of microparticles of at least one pharmaceutically active agent adhered to the surfaces of carrier particles, said particles being substantially larger than said microparticles and being water-soluble, and a bioadhesion and/or mucoadhesion promoting agent mainly adhered to the [surface s] surfaces of the carrier particles.--

Claim 7 has been amended as follows:

--7. (amended) A composition according to claim 6, wherein the bio/mucoadhesion promoting agent is selected from the group consisting of cellulose derivatives and comprising hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, [microcrystalline cellulose] and modified cellulose gum; crosscaramellose; modified starch; acrylic polymers comprising

carbomer and its derivatives; polyethylene oxide; chitosan; gelatin; sodium alginate; pectin; scleroglucan; xanthan gum; guar gum; poly-co-(methyl vinyl ether-maleic anhydride); and mixtures thereof.--

Claim 20 has been amended as follows:

--20. (amended) A [metod] method according to claim 19, wherein the pharmaceutically active agent is fentanyl or a pharmaceutically acceptable salt thereof.--